REMARKS

Applicants thank the Examiner for the review of the instant application. Claims 1-5 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed January 10, 2006. For the reasons set forth below, Applicants respectfully traverse.

Rejection Under 35 U.S.C. §101 – Utility

The PTO maintains its rejection of pending Claims 1-5 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Action. The PTO states that the claimed antibodies are not supported by either a substantial and specific utility or a well established utility.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO874 polypeptide is expressed at least two-fold higher in normal lung tissue compared to lung tumor;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding change in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO874 polypeptide is decreased in lung tumors compared to normal lung tissue, it is likely that the PRO874 polypeptide is decreased in lung tumors compared to normal lung tissue. Antibodies to polypeptides such as PRO874 which are differentially expressed in certain cancers are useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO states that Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) and LaBaer (Nat. Biotechnol. 21(9):976-7 (2003)) teach that most differential expression of as little as two-fold between disease and normal is attributable to disease-independent differences;

2. The PTO asserts that Haynes *et al.* (Electrophoresis, 19(11):1862-71 (1998)), Gygi *et al.* (Mol. Cell Biol. 19(3):1720-30 (1999)), Allman (Blood, 87(12):5257-68 (1996)), Chen *et al.* (Mol. Cell. Proteomics 1(4):304-13 (2002)) and Hancock (J. Proteome Res., 3(4):685 (2004)) establish that the skilled artisan would not know if or how expression of the PRO874 polypeptide would change in tumors because there are numerous levels of control of protein synthesis, degradation, processing and modification;

3. Consequently, the PTO concludes that one skilled in the art would be required to carry out further research to identify or reasonably confirm a "real world" context of use, and therefore the invention lacks a substantial utility.

Applicants respectfully submit that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

Applicants have established that the Gene Encoding the PRO874 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO874 gene is differentially expressed in lung tumors compared to normal lung tissue, and is therefore useful as a diagnostic tool for cancer, specifically lung cancer.

Applicants previously submitted a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. This declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue.

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual. That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. *First Grimaldi Declaration* at ¶ 5 (emphasis added).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between the pooled normal and tumor samples. This detected differential expression in pooled tumor samples compared to pooled normal samples represents a more generally relevant result compared to differential expression detected in samples from a single individual. He also states that the results of such gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He further states that if a "difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

In response, the PTO has relied on the reference by Hu *et al.* in which the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that

for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a published role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a published or known role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as molecular markers of cancer.

Applicants submit that a lack of known role for PRO874 in cancer does not prevent use of the polypeptide itself as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not

be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO874 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

In the present Office Action, the PTO cites several excerpts from Hu such as:

> [h]igh-throughput technologies, such as proteomic screening and DNA micro-arrays, produce vast amounts of data requiring comprehensive analytical methods to decipher the biologically relevant results. *Office Action* at 3, *quoting Hu* at Abstract.

> In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Id., quoting Hu* at 405, left column, first paragraph.

> It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful.... *Id.*, *quoting Hu* at 411-412.

As Applicants explained above, Hu studied differential gene expression and a known role in a disease. Thus, Hu's analysis of differential expression of a gene whose role in a disease is "relevant to the study" of the disease is completely different from Applicants' asserted differential expression of a gene for diagnostic purposes. Even if a gene does not have a role in causing a disease, and therefore is not relevant for a study of its role in the disease, this does not mean that the gene does not show a consistent and measurable change in expression in the cancer. Whether or not a differentially expressed gene has a known role in a disease or has biological relevance in studying a disease does not change the fact that differential expression of a gene and encoded polypeptide can be used in diagnosis of a disease. Accordingly, the PTO's assertion that expression of some genes is irrelevant to the study of a disease has no bearing on the diagnostic utility presently in question.

The PTO uses the publication by LaBaer to broaden its interpretation of Hu, stating:

> The examiner understands Hu's use of the term "biologically relevant," "biologically meaningful," or "relevant to the study" to include diagnostic relevance, which is supported by LaBaer. *Office Action* at 3.

The PTO points to a statement in LaBaer that:

> In the accelerating quest for disease biomarkers, use of high-throughput technologies, such as DNA microarrays and proteomics experiments, has produced vast datasets identifying thousands of genes whose expression patterns differ in diseased versus normal samples. Although many of these differences may reach statistical significance, they are not always biologically meaningful. For example, reports of mRNA or protein changes of as little as two-fold are not uncommon, and although some changes of this magnitude turn out to be important, most are attributable to disease-independent differences between samples. *Office Action* at 3 (emphasis added).

LaBaer is an unreviewed letter to the editor by an author of the Hu *et al.* article describing the automated literature searching tool used in the Hu *et al.* reference as discussed previously. LaBaer provides no further evidence than that provided in Hu, and provides no basis to consider processing and modification the results of Hu applicable to diagnostic utility of differentially expressed genes. Accordingly, LaBaer suffers from the same defects discussed above with respect to Hu *et al.* In particular, the biological correlations referred to in LaBaer are correlations with a published or known role for the gene in the disease. As discussed previously, with respect to Hu *et al.*, the results retrieved by the automated literature searching tool of Hu as described in LaBaer reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is differentially expressed in tumors to serve as a disease marker.

In addition, it is important to note that Applicants are not relying on microarray data as discussed in Hu and LaBaer. Instead, they are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. In a recent study by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), the authors used microarray analysis combined with proteomic analysis using two-dimensional gel electrophoresis to examine changes in gene expression in leukemia cell lines, just as discussed in LaBaer. The authors report that "[c]omparison of microarray and proteomic expression profiles showed poor correlation. Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction [RT-PCR], Western blotting and functional assays, on several genes and proteins, nonetheless, confirmed that there is indeed good correlation between mRNA and protein expression." Kuo *et al.* at Abstract (emphasis added) (attached as Exhibit 1). Thus, even if accurate, Hu and LaBaer's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

Moreover, LaBaer is silent regarding the reliability of pooled samples, and whether or not differential expression in pooled samples are susceptible to disease-independent differences between samples. The PTO's concern that "it is unknown if the PRO874 transcript differences are disease-dependent or disease-independent" is addressed by the statement in the first Grimaldi Declaration that "DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual." *First Grimaldi Declaration* at ¶ 5. LaBaer provides no reason to expect that differential expression in pooled samples is attributable to disease-independent differences between samples. Thus, LaBaer does not provide a basis for doubting Applicants' differential expression data. As such, there is no evidence that one skilled in the art would question whether the differential expression of PRO874 mRNA in pooled samples was disease-dependent or disease-independent.

Thus, nothing in either LaBaer or Hu mentions "diagnostic relevance" and nothing in these references purports to identify a threshold differential expression level to establish the relevance of a diagnostic marker. Hu compares differential expression levels with a published or known role for a gene in disease, as found by automated literature-mining software. LaBaer comments on the publication by Hu, and does not provide any evidence indicative of "diagnostic relevance" in differential gene expression. In addition, both Hu and LaBaer are commenting on the use of microarrays, a technique which is less accurate and reliable than the technique used by Applicants. Moreover, LaBaer and Hu are silent regarding any relevance of data generated using pooled normal and tumor samples, which were the samples analyzed in Applicants' Example 18. Accordingly, even if LaBaer and Hu were directed to differential expression levels that established "diagnostic relevance," such teachings would not be relevant to the data provided in Example 18 because such teachings would not be directed to data generated using pooled normal and tumor samples by PCR analysis.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establishes that there is reliable data reporting at least a two-fold difference in PRO874 mRNA between lung tumor tissue and normal lung tissue. Therefore, the expression levels of the PRO874 gene can be used, alone or in combination with other tools, to distinguish lung tumor tissue from normal lung tissue.

The PTO's Evidence is Not Relevant to Determining Whether a Change in mRNA Level for a Particular Gene lead to Corresponding Change in the Level of the Encoded Protein

Applicants turn next to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence that of differential expression of the mRNA for the PRO874 polypeptide in lung tumors, it is likely that the PRO874 polypeptide is also differentially expressed; and antibodies to proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO cites Haynes *et al.* (Electrophoresis, (1998) 19(11):1862-71), Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30), Allman (Blood, 87(12):5257-68 (1996)), Chen *et al.* (Mol. Cell. Proteomics 1(4):304-13 (2002)) and Hancock (J. Proteome Res., 3(4):685 (2004)) as support for its argument that the skilled artisan would not know if or how expression of the PRO874 polypeptide would change in tumors because there are numerous levels of control of protein expression. To support this assertion, the PTO selects a few quotes from each of the references without considering what the references teach as a whole. Applicants submit that when the entire reference is considered, none of Haynes, Gygi, Hancock, Chen or Allman support the PTO's position.

Haynes studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See Haynes* at 1863. Haynes did not examine whether a change in transcript level for a particular gene led to a change in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

The PTO has focused on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. Thus, Haynes showed that in yeast, similar steady-state mRNA

levels for different genes did not universally result in equivalent steady-state protein levels for the different gene products, and that similar steady-state protein levels for different gene products did not universally result from equivalent steady-state mRNA levels for the different genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding steady-state mRNA transcript when looking at the level of transcripts across different genes.

Importantly, Haynes did not say that for a single gene, a change in the level of mRNA transcript is not positively correlated with a change in the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for a particular gene leads to a corresponding increase or decrease for the encoded protein. Haynes did not study this issue and says absolutely nothing about it. One cannot look at the steady-state level of mRNA across several different genes to investigate whether a change in the level of mRNA a particular gene leads to a change in the level of protein for that gene. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's rejection of Applicants' asserted utility.

The same is true of Gygi *et al.*, a study on which the Haynes references is based. Like Haynes, the Gygi reference looked at steady-state levels of mRNA across different genes, not changes in mRNA levels for a single gene. Thus, when Gygi *et al.* state that "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data," the authors are referring to correlations between steady-state levels of mRNA and protein across different genes, not a correlation between a change in mRNA level and a change in protein level for the same gene and corresponding protein. Therefore, for the same reasons that Haynes is not relevant to Applicants' asserted utility, Gygi likewise offers no support for the PTO's rejection of Applicants' asserted utility.

Statements by Haynes and Gygi relied on by the PTO regarding the importance of posttranslational controls in determining the amount of protein are not relevant to Applicants' asserted utility as the following quote illustrates:

> The observed level of correlation between mRNA and protein expression levels suggest the importance of posttranslational mechanisms controlling gene expression. Such mechanisms include translational control .. and control of

> protein half-life.... Since these mechanisms are also active in higher eukaryotic cells, we speculate that there is no predictive correlation between steady-state levels of mRNA and those of protein in mammalian cells. *Gygi* at 1727 (emphasis added).

The above-underlined sentence illustrates how Haynes and Gygi are irrelevant to Applicants' assertions. Applicants have asserted that increasing or decreasing (*i.e.*, changing) the level of mRNA for a particular gene leads to a respective increase or decrease (*i.e.*, change) for the corresponding protein. Gygi states that the steady-state (*i.e.*, constant) levels of various mRNAs do not correlate with the steady-state (*i.e.*, constant) levels of the corresponding polypeptides when a correlation is sought across different genes because posttranslational controls have different influences on different genes. In contrast, Applicants assert that in general, an increase or decrease (*i.e.*, change) in mRNA levels for the same gene leads to a respective increase or decrease (*i.e.*, change) for the corresponding polypeptide. Neither Haynes nor Gygi reported anything regarding changes in mRNA levels or changes in polypeptide levels for the same gene. Accordingly, the results of Haynes or Gygi are not relevant to Applicants' assertions regarding the relationship between changes in mRNA levels and the corresponding polypeptide levels. As such, Haynes and Gygi cannot support the PTO's holding of a lack of utility for the claimed antibodies.

The PTO cites Allman *et al.* (Blood, 87(12):5257-68 (1996)) as supporting Haynes and Gygi, quoting a portion of Allman which states that "germinal center B cells express dramatically more BCL-6 protein than resting B cells, despite similar BCL-6 mRNA levels in the two cell populations." *Office Action* at 4, *quoting Allman* at 5257, right column. Applicants submit that Allman is not contrary to Applicants' asserted utility because Allman does not teach that a change in mRNA level does not lead to a corresponding change in level of the encoded polypeptide – at best Allman teaches that mechanisms other than increasing mRNA levels can lead to increased protein levels. This is not contrary to Applicants' assertion.

Applicants disclose in Example 18 differential expression of PRO874 mRNA in lung tumor tissue compared to normal lung tissue. Applicants submit that one skilled in the art would expect that a change in mRNA levels would generally lead to a corresponding change in levels of the encoded polypeptide. Applicants make no assertions regarding expected changes in protein levels when mRNA levels are unchanged, and evidence of changes in protein levels when mRNA levels are unchanged has no relevance to Applicants' assertion.

Allman does not stand for a position contrary to Applicants' asserted utility. If anything, Allman supports Applicants' utility. Allman states that "BCL-6 protein was readily detectable in germinal center cells (Fig. 6A) and in B-cell lines that express BCL-6 mRNA (Fig. 6A, BJAB and RL), but not in B-cell lines that express little or no BCL-6 mRNA (Fig 6A, VDSO)." *Allman* at 5263, right column. Thus, Allman teaches that for cells expressing higher levels of BCL-6 mRNA, BCL-6 polypeptide levels also were higher, relative to BCL-6 polypeptide levels in cells that expressed lower levels of BCL-6. Nowhere does Allman teach that a change in mRNA levels would not lead to a corresponding change in levels of the encoded polypeptide. Accordingly, Allman is not contrary to Applicants' asserted utility and does not support the PTO's position, and provides teachings consistent with Applicants' asserted utility.

Furthermore, Applicants maintain that Allman's discussion of the observed protein levels supports Applicants' assertion that it is well-established in the art that in general, the level of protein is positively correlated to the level of mRNA. In the discussion of their finding that mRNA and DNA levels were not correlated, Allman refers to the discovery as a "striking dichotomy." *Allman et al.* at 5265, right column. They also state that "an *unanticipated* finding was that the higher BCL-6 protein levels...could not be fully accounted for by increased mRNA expression." *Allman et al.* at 5267, left column (emphasis added). Both of these statements indicate that normally, protein expression is correlated to mRNA levels, and their findings to the contrary were unexpected for that reason.

The PTO also cites Chen *et al.* for support for the assertion that polypeptide levels cannot be accurately predicted from mRNA levels. *See Office Action* at 3-4. In Chen, the authors examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and 9 non-tumor lung samples.

Like Haynes and Gygi, Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across the different genes. Thus, Chen's statement that "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" is referring to a correlation between steady-state mRNA levels and protein levels across <u>different</u> genes. As discussed above with respect to Haynes and Gygi, this measurement of a correlation across different genes is not

relevant to Applicants' asserted utility which relies in part on a correlation between changes in a gene's expression level and changes in the level of the encoded protein.

In addition to looking at global correlations across genes, Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 21.4% (21 of 98) of the genes showed a statistically significant correlation between protein and mRNA expression.

Chen provides scant evidence to counter Applicants' asserted utility for the claimed antibodies because when examined closely, portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between changes in mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level. *Chen* at 306, right column. Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The only data showing a change in mRNA level in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The PTO relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels because of posttranslational regulation. However, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level.

This can be understood by again turning to Figures 2A-2C. As noted above, where a wide range of mRNA expression levels are seen, a correlation between mRNA and protein levels was observed. However, if one examines the data points within a small range of mRNA levels for these same genes, e.g. 500-600 or 5000-6000 in Figs. 2A-2C, it is clear that a correlation would not be detected for the data within this range. This does not mean that a correlation between changes in mRNA and protein does not exist for these genes, as is evident when larger changes in mRNA expression are included in the analysis. Instead, this indicates that for relatively small changes in mRNA, any correlation is masked by imprecision in the measurements.

Chen's experiment compared mRNA levels vs. protein levels across samples without selecting mRNA that showed a difference in expression level. And unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue. Since almost all samples tested by Chen were from the same type of tissue, few substantial variations in the level of mRNA or protein for a particular gene across the samples tested would be expected. Instead, it would be expected that most genes examined by Chen would have similar mRNA or protein levels across the samples. Figures 2A-2C of Chen demonstrate that the methods utilized by Chen cannot detect correlations between mRNA and protein levels when only small differences in mRNA expression are observed, but a correlation is detected when larger differences in mRNA expression are observed.

Accordingly, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, this data also explains the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen. Thus, even given Chen's inability to detect a correlation between mRNA and protein in some genes, Chen's results do not refute Applicants' position.

Instead, Chen supports Applicants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater. In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett. 2000; 480:2-16) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not

relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue and citation of Anderson and Seilhamer (Electrophoresis 1997; 18:533-37) and Gygi *et al.* (Mol. Cell. Bio. 1999; 19:1720-30) offer no support for the PTO's position.

In conclusion, for the reasons discussed above with respect to Haynes and Gygi, portions of Chen are simply irrelevant to the discussion of whether or not the changes in mRNA lead to corresponding changes in the level of encoded protein because Chen was looking at mRNA and protein levels across different genes. The remainder of Chen offers little or no support for the PTO's position since Chen did not examine genes where a change in mRNA level was known to occur. In the three cases where it is certain that changes in mRNA level did occur, there is a correlation between the changes in the level of mRNA and the changes in the level of the corresponding protein.

Even if the results in Chen supported the PTO's argument, which they do not as discussed above, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between changes in mRNA level and changes in protein level for an individual gene. As the PTO points out and Applicants acknowledge, there are other non-transcriptional mechanisms for regulating gene and protein expression (*i.e.*, post-transcriptional regulation of genes, translation efficiency, etc.). However, as shown by the declarations, references, and textbooks discussed below, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between changes in mRNA levels and changes in protein levels for a particular gene.

The PTO further cites Hancock as support for the assertion that protein expression levels are not predictable from mRNA expression levels. Hancock states that "the markers that are generated by proteomics are not always consistent with the markers that are generated from expression profiling." *Office Action* at 4, *quoting Hancock* at second paragraph. Read in context, this paragraph does not support the PTO's position. The paragraph following the one quoted above states: "This Editor believes that proteomics is at too early a stage for this new technology to have generated a quality list of [bio]markers." *Hancock* at third paragraph. Hancock goes on to indicate the importance of "improvements in emerging proteomics technology." *Id.* Thus, Hancock is explaining that proteomics has not developed sufficiently to

be a reliable method of generating biomarkers. Therefore, Hancock is attributing incongruities between expression profiling and proteomics to shortcomings in proteomics methods, and not to actual, accurately measured protein and mRNA levels in a cell.

In sum, Applicants submit that the evidence cited by the PTO are not contrary to Applicants asserted utility since none of Haynes, Gygi, Allman, Chen and Hancock would lead one skilled in the art to question the assertion that a change in mRNA levels generally leads to a corresponding change in polypeptide levels.

Applicants' Evidence Establishes that a Change in mRNA Level for a Particular Gene leads to a Corresponding Change in the Level of the Encoded Protein

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, a copy of the declaration of Paul Polakis, Ph.D., excerpts from the Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002). The details of the teachings of these declarations and references, and how they support Applicants' asserted utility, are of record and will not be repeated here.

In addition to the supporting references previously submitted by Applicants, Applicants submit the following references to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

In a comprehensive study by Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (previously submitted with IDS, attached hereto as Exhibit 2), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of

40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 3) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 4) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 5) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven

cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 6) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20Salpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 7) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 8). In a previous study, the authors

investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Mizrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 9) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 10), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, e.g. a decrease, lead to a corresponding change in the level of the encoded protein, e.g. a decrease.

In an article by Gou and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 11) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, e.g. an increase, generally leads to a corresponding change in the level of protein expression, e.g. an increase.

These studies are representative of numerous published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an additional 70 references (abstracts attached as Exhibit 12) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer indirect support of Applicants' asserted utility. As discussed in detail above, Applicants have challenged the relevance of references such as Haynes *et al.* and Chen *et al.* which do not attempt to examine the correlation between a change in mRNA level and a change in the level of the corresponding protein level. Because the PTO continues to rely on these references, Applicants are submitting references which report results that are contrary to the PTO's cited references and offer indirect support for Applicants' asserted utility.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract attached as Exhibit 13) the authors conducted a study of mRNA and protein expression in yeast which was nearly identical to the one conducted by Gygi *et al.* and reported in Haynes *et al.* Contrary to the results of the earlier study by Gygi, Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract.

In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 14) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 15) the authors examined the expression of three somatostatin receptors (SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a "good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 16) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 17) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 18) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 19) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases)." *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 20) which also support Applicants' assertion in that the references report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of 113 references in addition to the declarations and references already of record which support Applicants' asserted utility, either directly or indirectly. These references support the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.,* abstracts attached as Exhibit 21). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO874 mRNA is differentially expressed in lung tumors compared to normal lung tissue , the PRO874 polypeptide will likewise be differentially expressed in lung tumors. This differential expression of the PRO874 polypeptide makes the claimed antibodies useful as diagnostic tools for cancer, particularly lung cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies related to PRO874. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO874 gene and polypeptide in certain types of cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that it is more likely than not that the PRO874 polypeptide is differentially expressed in lung tumor tissue compared to normal lung tissue. These data are strong evidence that the PRO874 polypeptide is associated with lung tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO874 polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly lung tumors, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Utility – Conclusion

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (same); *Nelson v. Bowler*, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same). In addition, utility need only be shown to be "more likely than not true," not to a statistical certainty. *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility, one skilled in the art would not know how to use the claimed invention. *See Office Action* at 17.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Thus, since the enablement rejection is based on the rejection of the claims as lacking utility,

Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Rejections under 35 U.S.C. § 112, first paragraph – Written Description, New Matter

The PTO maintains its rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The PTO argues that there is no written support for the limitation "amino acids 34-321 of SEQ ID NO: 10."

As amended, the Claim 1 recites "An isolated antibody that specifically binds to the polypeptide having the amino acid sequence of amino acids 34-321 of SEQ ID NO: 10." For the reasons of record, Applicants submit that the this claim language is supported by the specification as filed, and does not constitute new matter.

In response to Applicants' previous arguments, the PTO states that "Applicants have not adequately described 'amino acids 34-321 of SEQ ID NO:10' because there is no evidence of record that amino acid #34 is employed as a start site.... [T]he generic disclosure of what may be possible or conceivable does not convey with reasonable clarity to those skilled in the art that Applicants were in possession of the invention now claimed." *Office Action* at 18-19.

Applicants submit that looking at the sequence, it would be apparent to any skilled artisan that the first methionine in SEQ ID NO:10 is likely the start methionine, and that would be sufficient evidence to convey with "reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." *M.P.E.P.* §2163.02 (emphasis added).

For the reasons of record and those stated above, Applicants submit that the PTO has failed to meet its initial burden of "presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." *M.P.E.P.* §2163.04 (internal citations omitted, emphasis added). Applicants request that the PTO reconsider and withdraw the written description rejections under 35 U.S.C. §112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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